Population Dynamics of Tay-Sachs Disease. I. Reproductive Fitness and Selection

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INTRODUCTION

TAY-SACHS DISEASE (TSD) or infantile amaurotic familial idiocy is a hereditary disease of lipid storage in which the sphingolipid ganglioside accumulates in the cytoplasm of the neurons of the brain. It is characterized by progressive degeneration of cerebral function which commences soon after birth and ends in death usually within the first or second year of life. The disease has been demonstrated to be due to the homozygous condition of an autosomal recessive gene, apparently with complete penetrance (Slome, 1933; Ktenidés, 1954; Kozinn, Wiener, and Cohen, 1957; Aronson, Aronson, and Volk, 1959). When the disease was first recognized, it was thought to be an exclusively Jewish disorder, but verified cases in non-Jewish infants were reported later. These cases have become increasingly numerous in the literature in recent years, and Myrianthopoulos (1962) showed that fully one-third of cases in the United States are of non-Jewish origin.

It is further well established that TSD is more frequent among the Ashkenazi Jews than among other Jewish (Sephardi) groups and non-Jewish populations. (See above investigators as well as Goldschmidt *et al.*, 1956; Goldschmidt, Ronen, and Ronen, 1960; Goldschmidt and Cohen, 1964). Although considerable literature has recently been devoted to the genetics, epidemiology, and demography of the disease, the major problem of why the TSD gene, despite its mass elimination, is found in such high frequency among the Ashkenazi Jews is still unresolved. The purpose of this paper is to examine the mechanisms by which the frequency of so lethal a gene could have become elevated and then maintained at the present high level and to present evidence which suggests that one such mechanism may have been responsible for this phenomenon.

Estimates of the frequency of the TSD gene among Jews and among non-Jews are in rather close agreement (Table 1). In the United States, the disease occurs once in approximately 6,000 Jewish births and once in approximately 500,000 non-Jewish births. On the basis of this birth incidence, it is estimated that one of 40 Jewish persons and one of 380 non-Jewish persons is heterozy-

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TABLE 1. ESTIMATES OF THE FREQUENCY OF THE TSD GENE AMONG JEWS AND NON-JEWS

Source	Region	Years surveyed	Birth incidence of TSD	TSD gene frequency	Carrier frequency
Among Jews					
Goldschmidt *et al.* (1956)	Israel	1948–1952	0.00020	0.014	0.028
Kozinn, Wiener, and Cohen (1957)	New York City	1944–1955	0.00012	0.011	0.022
Myrianthopoulos (1962)	United States	1954–1957	0.00016	0.013	0.025
Aronson (1964)	New York City	1951–1962	0.00023	0.015	0.030
Among Non-Jews					
Kozinn, Wiener, and Cohen (1957)	New York City	1944–1955	0.0000022	0.0015	0.003
Myrianthopoulos (1962)	United States	1954–1957	0.0000017	0.0013	0.0026
Aronson (1964)	New York City	1951–1960	0.0000026	0.0016	0.0032

gous for the TSD gene. Thus, the gene frequency is about ten times higher and the birth incidence 100 times higher among Ashkenazi Jews than among non-Jews. A difference of the same magnitude apparently exists between the Ashkenazi Jews and the other Jewish groups in Israel and the Eastern Mediterranean. The birth incidence of TSD among the Sephardic and Oriental communities of the Middle East and North Africa appears to be even lower than that found in non-Jewish Europeans and Americans.

The following mechanisms can be invoked to explain the differential frequency of TSD and the gene responsible for it in the two population groups: (1) differential breeding pattern; (2) genetic drift; (3) differential mutation rate; (4) differential fertility of the heterozygote, and (5) a combination of any of these mechanisms.

Differential breeding pattern would involve such socially conditioned forces as intermarriage between genetically different groups and close inbreeding within a group. It may be argued that the high frequency of TSD among the Ashkenazi Jews represents a repeated introduction of genes through local intermarriage with non-Jews which was subsequently abetted by inbreeding and genetic drift. This is improbable since we have no evidence that TSD was present in any appreciable frequency in the non-Jewish Polish, Lithuanian, and Russian populations among whom the Jews settled after the diaspora. It is from these areas that most of the ancestors of the Jewish TSD cases in the United States appear to have come (Aronson and Volk, 1962).

Consanguinity data are not helpful and merely reflect gene frequency levels in the two groups. In general, with rare recessive genes, the consanguinity rate among parents of affected children bears an inverse relationship to the gene frequency. This is precisely what we find in our data (Myrianthopoulos, 1962). In a series of 83 TSD families, the first-cousin marriage rate among parents of Jewish infants was 1.78%, while among the parents of non-Jewish infants it was 7.70%. Consanguinity of varying degrees was found in 5.26% of parents of Jewish infants and in 11.12% of parents of non-Jewish infants. First-cousin

marriages among the Ashkenazi population of Israel range between 1% and 2% which is not significantly different than the rate for the Jewish population in the United States (Goldschmidt, Ronen, and Ronen, 1960), while that of the Sephardic and Oriental communities is extraordinarily high, ranging from 7% to 29% (Goldschmidt and Cohen, 1964). Yet, the birth incidence of TSD in these latter communities is very low, perhaps even lower than that found in non-Jewish European populations. It might be argued that the high consanguinity rate of the Sephardic Jews has served to deplete the gene from this population rather rapidly and the process must be continuing. However, this cannot account for the low frequency of the gene in non-Jewish populations.

The argument for genetic drift is weak enough at the outset, for drift, in the strict sense, is supposed to have its random effect on the frequencies of near neutral genes or slightly unfavorable ones. It is, perhaps, permissible to stretch the operational definition of drift to include lethal genes, such as the TSD gene, although we do not know of a precedent.

Genetic drift could be held partly accountable for the rise of the TSD gene at a very high frequency if it could be shown that the Jewish isolates of Europe, especially of northeastern Poland and the surrounding areas, were composed of very small marriageable populations without social contact with neighboring communities. There is sufficient historical commentary, however, to indicate a fertile intercommunication between these religious-cultural communities. In a review of the places of birth of the foreign-born Jewish grandparents and great-grandparents of a large number of TSD cases, Aronson (1964) found that about 40% of the grandparent marriages were between coreligionists born in different countries, 49% were between individuals born in the same East European country but in separate cities, and only 11% of the marriages were between individuals born in the same community. These figures indicate that the grandparents and great-grandparents of children with TSD, at least as far back as 1850, were sufficiently mobile to choose marriage partners in centers beyond their own immediate communities. Further, from our demographic studies of these areas, it appears that the Jewish communities were large enough to support synagogues and schools and to engage in active social life. Many thousands of Jews lived in northeastern Europe for many generations. We can find no evidence for circumstances which theoretically might favor drift, such as migration of small groups, famine, disease, or war, affecting all or a large number of these Jewish communities simultaneously. No doubt, such circumstances existed at one time or another, within one community or another. But even under conditions of complete genetic isolation, random fluctuation of the TSD gene in some communities must have been balanced in other communities. And our demographic data show that the Jews of the United States, among whom our observations were made, emigrated not from a few selected communities but from hundreds of cities, towns, and villages of northeastern Europe (S. M. Aronson and N. C. Myrianthopoulos, unpublished data). On the basis, then, of what is known, it is unreasonable to hold genetic drift as the predominant factor responsible for the elevation of the TSD gene frequency among the Ashkenazi Jews.

The possibility of differential mutation rate is equally unlikely. The mutation rate needed to account for the estimated frequencies of the TSD gene would be equal to the frequency of the trait in the population, i.e., about one mutation per 6,000 gametes per generation among Jews and one mutation per 500,000 gametes per generation among non-Jews, which is absurd. All available evidence indicates that mutation rates of specific loci tend to be rather constant within species.

The Possibility of Heterozygote Advantage

The possibility of heterozygote advantage was considered earlier (Myrianthopoulos, 1962) but not pursued because of lack of adequate control data to test it. Heterozygote advantage would provide an adequate explanation for the differential increase of the TSD gene if it could be shown that Jewish heterozygotes were more fertile than the Jewish homozygous normal and thus were able to transmit the mutant gene to the next generation differentially.

The magnitude of the selective advantage required by heterozygotes in order to maintain the frequency of the lethal TSD gene at such a high level among the Ashkenazi Jewish population is given by

$$S = q/(1 - q)$$

where S is the selection coefficient against the normal homozygote. Substituting the estimated frequency of the TSD gene among the Ashkenazi Jews of 0.0126,

$$S = 0.0126/(1 - 0.0126) = 0.0128$$

and the fitness of the three genotypes is

$$\begin{aligned} TT &= 1 - S = 0.9872 \\ Tt &= 1 \\ tt &= 0 \end{aligned}$$

which means that a selective advantage of about 1¼% on the part of heterozygotes is sufficient to maintain the gene at equilibrium despite its mass elimination via the TSD homozygotes. In order to determine if this is the case in the TSD population, it is necessary to collect and examine information on the fertility of Jewish women, particularly those known to be carriers of the TSD gene.

Our study population could, of course, be the parents of children with TSD, since these are both known to be heterozygous. But their total reproductive performance is almost certain to be biased by the birth of a child with a lethal hereditary disease and by the knowledge that there is a high probability of repeating this misfortune in subsequent pregnancies. This bias is quite evident from birth order analysis of 188 Jewish TSD cases in 150 sibships of two or more, shown in Table 2, calculated by the method of Haldane and Smith (1948). In theory, the test makes use of A, the sum of birth ranks of all affected sibs, and compares it with its theoretical mean value, calculated on the assumption that there is no birth rank effect. In practice, the arithmetic is

TABLE 2. EFFECT OF BIRTH RANK AMONG TSD JEWISH CASES

Sibship size	Birth rank 1	2	3	4	5	6	7	8	Total
2	28	65							93
3	16	15	35						66
4	4	2	4	7					17
5	1	1			3				5
6									
7	1			1		1	1		4
8						1	1	1	3
Total	50	83	39	8	3	2	2	1	188

$6A = 2646$ $\quad 6A - m = 363$

$m = 2283$ Number of standard

$s^2 = 3721$ deviations exceeding mean = 363/61 = 5.95

$s = 61.0$

simplified if *6A* is tested in place of *A*. Both *6A* and its variance are integers and are given in table form in the article by Haldane and Smith. Among the Jewish TSD cases, *6A* exceeds its mean by almost six standard deviations. A similar birth rank effect, although not as striking, is found among non-Jewish TSD cases, where *6A* exceeds its mean by almost three standard deviations. This finding is almost predictable and does not really indicate that birth rank effect is a phenomenon of biological significance. It merely reflects the bias which is introduced by a voluntary truncation of family size when a child with TSD has been produced. This effect is much more pronounced among the Jewish cases, since Jewish parents who have a TSD child are more aware of the social and medical consequences of such an occurrence than are non-Jews generally, and the eugenic problem concerns them more acutely.

An unbiased estimate of the fertility of the unsuspecting heterozygotes, who unknowingly perpetuate the gene, can be obtained by assessing the fertility of the grandparents of the affected children. It may be assumed that at least one maternal and one paternal grandparent of an affected child is a heterozygote. It can also be assumed that by the time the TSD homozygote (grandchild) has been identified, the fertility of the grandparents will have been completed. The fertility can be estimated by determining the number of surviving offspring, that is, the sibships containing the parents of the affected, and comparing with an appropriate control group.

SOURCE OF DATA AND METHODOLOGY

The data for this study came from two sources: from screening by one of us (N.C.M.) of death certificates from the Bureau of Vital Statistics assigned to rubric 325.5 (*mental deficiency, other and unspecified types*) of the International List of Causes of Death, for deaths which occurred in the United States during the years 1954–1957, inclusive, and from a case registry of cerebral sphingolipidoses which was begun by one of us (S.M.A.) in 1952.

The first source, which constitutes as complete ascertainment of cases as possible for the four year period, yielded 89 cases of TSD, 58 in children of

TABLE 3. TSD AND CONTROL SIBSHIPS

	Number of sibships	Total number of siblings
TSD		
U. S. born	322	1008
Non-U. S. born	66	236
Total	388	1244
Controls		
U. S. born	713	2436
Non-U. S. born	99	412
Total	812	2848

Jewish parents, 29 in children of non-Jewish parents and two cases in children with one Jewish and one non-Jewish parent. The second source provided 296 cases in 242 families, mostly from the New York City area, and contains a much larger proportion of Jewish cases. From this source, 226 cases were in children of Jewish parents, 35 in children of non-Jewish parents, and 35 in children with mixed or doubtful parentage. Over 85% of cases recorded as having died from 1954 through 1957 were picked up independently through the second source. (For details about the method and criteria for selection of cases, see Myrianthopoulos, 1962, and Aronson, 1964.)

The unit of this investigation is not the affected individual but the family, particularly the sibship of the parents of the affected child. By personal contact and mailed questionnaire, we sought to obtain from the parents precise and detailed information concerning dates of birth and death and neurological conditions of siblings, parents, aunts and uncles, grandparents, and first cousins of these cases, as well as other demographic data. We were able to collect all the required information for 194 families of Jewish cases and 47 families of non-Jewish cases.

In this paper, we are concerned exclusively with the sibships of the Jewish TSD parents, comprising 388 sibships with 1,244 total siblings. The distribution of the sibships of the parents of Jewish cases, which include the parents themselves, and the distribution of the control sibships, to be described below, is given by place of birth in Table 3. These are separated into U. S. born and non-U. S. born for purposes of analysis, since it is conceivable that a heterozygote effect might exist in the one group and not in the other.

The ordinarily difficult task of selecting the proper control proved to be straightforward in our case. The lack of adequate demographic and fertility data for the Jewish population of the United States dictated the only logical alternative: to obtain a population sample which would be representative of the United States Jewry and comparable to our own TSD sample with regard to those variables which were required for comparison and control.

The sources of the control sibships were seven synagogues (Philadelphia, Pennsylvania; White Plains, Brooklyn, and Lawrence, New York; Bridgeport and Trumbull, Connecticut; and Boston, Massachusetts) as well as some fraternal societies (not affiliated with synagogues) from the New York City area.

The selected controls were married couples with children among whom Tay-Sachs disease had not occurred. Thus, the claim can be made that the control sample is representative of the urban and suburban Jewish population of the northeastern United States, corresponding approximately with the TSD sample in country of birth, age, number of children, religious-cultural background, socioeconomic level, and geographic distribution. The co-operation of these people was entirely voluntary, and it was secured after an appeal and an explanation of the general scope of the study. The specific aim, i.e., the comparison of fertility and test for heterozygote advantage, was not discussed with them. Each control was asked to complete a confidential questionnaire, giving much the same information as that obtained from the parents of the TSD cases. This information was collected from 406 couples comprising 812 sibships with 2,848 total siblings. Their distribution is shown in Table 3.

One possible bias which could weaken the power of the comparison stems from the well known correlation of family size of closely related individuals. The family size of a propositus group could be greater than that of the control group to the extent that there is a correlation between the propositus sibship size and the sibship size of the parental generation. Unfortunately, it is impossible to demonstrate presence or absence of correlation between sibship size of our index cases and that of the parents because the parents have not completed their reproduction in most instances and also because Jewish parents of TSD children tend to curb their reproduction, as was demonstrated by the birth rank test (Table 2). Information about the siblings of the grandparents, almost all of whom were born in Europe and most of them now dead, is very scanty; therefore, a correlation at this level cannot be attempted either. The only positive statement that can be made is that the selected controls had, on the average, no fewer children than the TSD parents and that both groups must have come from relatively large families. We feel that this bias, if it has entered at all in the selection of the control group, is not of sufficient magnitude to influence the results.

RESULTS

Selective advantage in modern genetics is expressed as a function of relative reproductive fitness. The concept of relative reproductive fitness of individuals with specific traits, or carriers of specific genes, although simple enough, has proven surprisingly difficult in practical application because the genetic situations on which the concept of fitness has a deciding bearing are often variable and subtle. Relative fitness in its simplest terms can be expressed as the ratio of the mean number of children of two groups, an affected group and a control group. In practice, such a ratio is not easy to derive. The affected group, for example, may not have completed their reproduction. There is no universal definition of the unit of fertility, neither need there be; further, there is the proverbial problem of what constitutes an adequate control group for a particular genetic situation and under a particular set of circumstances. These problems and their many ramifications have been dealt with extensively in methodological papers (see Krooth, 1955; Reed, 1959).

TABLE 4. FERTILITY OF JEWISH TSD AND CONTROL FAMILIES

Decade of birth:	1890–1899		1900–1909		1910–1919		1920–1929		1930–1939		1940–1949	
	TSD	Control	TSD	Control	TSD	Control	TSD	Control	TSD	Control	TSD	Control
U. S. born												
Number of sibships	2	45	13	71	81	210	136	249	84	127	6	11
Total siblings	7	217	58	338	326	803	382	732	215	322	20	24
Number dying before age 21	0	25	2	31	11	43	4	37	2	15	0	0
Number surviving to age 21	7	192	56	307	315	760	378	695	213	307	20	24
Average total	3.50	4.82	4.46	4.76	4.02	3.82	2.81	2.94	2.56	2.54	3.33	2.18
Average surviving to age 21	3.50	4.26	4.31	4.32	3.88	3.62	2.78	2.79	2.54	2.42	3.33	2.18
Non-U. S. born												
Number of sibships	2	20	5	22	14	25	30	23	15	8	0	1
Total siblings	13	121	27	118	49	84	103	66	44	21		2
Number dying before age 21	0	5	2	14	5	4	3	11	4	0		0
Number surviving to age 21	13	116	25	104	44	80	100	55	40	21		2
Average total	6.50	6.05	5.40	5.36	3.50	3.36	3.43	2.87	2.93	2.62		
Average surviving to age 21	6.50	5.80	5.00	4.72	3.14	3.20	3.33	2.39	2.67	2.62		

TABLE 5. RATIO OF ADJUSTED FERTILITIES OF TSD GRANDPARENTS AND CONTROLS

U. S. born				
Total siblings	$\frac{\text{TSD}}{\text{Controls}}$	=	$\frac{1010.30}{1007.22}$	= 1.0031
Siblings surviving to age 21	$\frac{\text{TSD}}{\text{Controls}}$	=	$\frac{991.25}{953.70}$	= 1.0394
Non-U. S. born				
Total siblings	$\frac{\text{TSD}}{\text{Controls}}$	=	$\frac{235.85}{211.34}$	= 1.1160
Siblings surviving to age 21	$\frac{\text{TSD}}{\text{Controls}}$	=	$\frac{221.91}{191.00}$	= 1.1618

In this study, the definition of relative fitness of the heterozygous carriers for the TSD gene is reduced to its simplest terms because the grandparents whose fertility is assessed have completed their reproduction at the time of the study. The unit of fertility is defined as a livebirth who has survived to reproductive age, for which 21 years is considered a reasonable lower limit; the analysis, however, will also include all livebirths.

The completed reproductive performance of the TSD heterozygotes, represented by the sibships of parents of TSD children and that of the controls, is shown in Table 4. The number of sibships, total number of siblings, number of siblings surviving through age 21, and average number of total and surviving siblings are given by decade of birth of each "proband" TSD and control parent. These are further subdivided according to the U. S. born versus non-U. S. born dichotomy. The "proband" parents are distributed by decade of birth so that the effects of fertility trends over a span of half a century would not obscure the over-all heterozygote effect, if any, and the contribution of each decade may be properly evaluated and weighted.

From a cursory inspection of Table 4, it becomes evident that there are some rather consistent differences between the TSD and control sibships, especially among the non-U. S. born, favoring the TSD sibships. These differences are clearly seen when the mean number of total and surviving siblings is adjusted for sample size. Table 5 shows the ratio of adjusted reproductive performance of TSD heterozygotes and controls. The adjustment was made by multiplying the number of control sibships by the average number of TSD siblings in each decade, and vice versa, and summing up over all decades. This represents a simple but true measure of fertility, and it shows that in all four categories the ratio is in favor of the TSD heterozygote. Its highest deviation from unity, about 16%, is in the category of non-U. S. born who survive to age 21; it decreases in the two following categories and becomes negligible among the total U. S. born siblings.

The differences which resulted after adjustment for sample size are, as expected, small and not statistically significant. The significance test which was

TABLE 6. COMPARISON OF MEAN FERTILITY OF TSD HETEROZYGOTES AND CONTROLS

Values of t for each of four categories in each decade

Decade of birth	U. S. born		Non-U. S. born	
	Total siblings	Surviving to age 21	Total siblings	Surviving to age 21
1890–1899	−0.87	−0.56	0.22	0.43
1900–1909	−0.50	−0.02	0.03	0.25
1910–1919	0.85	1.13	0.24	−0.01
1920–1929	0.87	−0.07	1.00	2.02
1930–1939	0.30	1.00	0.46	0.08
1940–1949	1.16	1.16		

TABLE 7. COMPARISON OF MEAN FERTILITY OF TSD HETEROZYGOTES AND CONTROLS

Weighted mean of t, its standard error, and standardized $\bar{t}$ in each of four categories

Categories	$\bar{t}_w$	$SE_{\bar{t}_w}$	$\bar{t}_w/SE_{\bar{t}_w}$	P
U. S. born				
Total siblings	−0.01	0.42	−0.02	0.9840
Siblings surviving to age 21	0.43	0.41	1.05	0.2937
Non-U. S. born				
Total siblings	0.40	0.46	0.87	0.3843
Siblings surviving to age 21	0.53	0.45	1.18	0.2380

considered as most appropriate for these data is a combination t test which combines separate t values for each decade, comparing the mean total siblings and those surviving beyond 21 years of the TSD sibships with the corresponding categories of the controls. The individual t values, shown in Table 6, were weighted by the inverse of their variances and summed over all decades, and a mean t was computed for each of the four categories: total U. S. born siblings, U. S. born surviving age 21, total non-U. S. born siblings, and non-U. S. born surviving age 21. The variance of t is given by

$$V_t = n/(n-2)$$

where n is the number of degrees of freedom. The weight of t is the inverse of its variance,

$$W_t = 1/V_t$$

Table 7 shows the weighted mean of t, its standard error, and the standardized $\bar{t}$ in each of the four categories, where

$$\bar{t}_w = \Sigma W_t t/\Sigma W_t$$

and

$$SE_{\bar{t}_w} = 1/\sqrt{\Sigma W_t}$$

TABLE 8. LOSS OF SIBLINGS NOT SURVIVING TO AGE 21, PER DECADE

Decade of birth	1890–1899	1900–1909	1910–1919	1920–1929	1930–1939	1940–1949
U. S. born						
TSD	0.00	0.03	0.03	0.01	0.01	0.00
Controls	0.11	0.09	0.05	0.05	0.05	0.00
Non-U. S. born						
TSD	0.00	0.07	0.10	0.03	0.09	0.00
Controls	0.04	0.12	0.05	0.17	0.00	0.00

TABLE 9. CHI SQUARE TEST OF DIFFERENCES IN SIBLINGS SURVIVING TO AGE 21 BETWEEN TSD AND CONTROL SIBSHIPS

Decade of birth	U. S. born χ^2	Non-U. S. born χ^2	Non-U. S. born χ	Total siblings χ^2
1890–1899	0.9	0.6	+0.78	2.0
1900–1909	2.0	0.5	+0.71	2.3
1910–1919	2.0	1.4	−1.18	0.6
1920–1929	11.5	9.9	+3.15	15.3
1930–1939	5.8	1.9	−1.38	1.9
	$\chi^2_5 = 22.2$	$\chi^2_5 = 14.3$	$\Sigma\chi = 2.08$	$\chi^2_5 = 22.1$
	$P < 0.001$	$P = 0.01$	$\Sigma\chi/\sqrt{n} = 0.93$	$P < 0.001$
			$P = 0.35$	

For n greater than 30, as is the case here, the distribution of $\bar{t}$ becomes very nearly normal, and the P values correspond to those of the standard normal variable. (For the best description of combination of tests of significance, see Hald, 1952.)

Although the differences in fertility are not significant, the apparent definite fertility gradient in the four categories suggests that differential survival might be an important component. Indeed, when the percentage loss in each decade is calculated (Table 8), the loss among controls, with only two exceptions, is higher—and survival to age 21 lower—than that among the TSD sibships.

The over-all difference in survival to age 21 between the TSD and control sibships is statistically significant (Table 9). The test procedure employed here is that of combining 2 × 2 tables for each decade in each category, for which chi squares were computed in the usual way. These were then added up to command n degrees of freedom. By this test, the differences in all three categories are highly significant. The procedure is legitimate in the categories U. S. born and total siblings because the sign of the difference between observed and expected is the same in all decades. In the non-U. S. born category, however, the percentage loss in the decades 1910–19 and 1930–39 is higher among the TSD siblings than in the controls. In order to account for the sign of the difference, values of χ insead of χ^2 were computed for each decade (Cochran, 1954). Since χ and, therefore, the sum of its independent values are normally distributed, the test statistic $\Sigma\chi/\sqrt{n}$ can be used and referred to the

normal curve tables. When computed in this way, the value of the normal deviate is not significant. This, of course, is a test for survival apart from that of fertility and measures the survival component in siblings of heterozygous parents, half of whom are expected to be heterozygous normal.

DISCUSSION

The failure to find statistically significant differences in fertility between TSD heterozygotes and controls does not invalidate the argument of heterozygote advantage. The predicament here is that in order to be statistically significant, the differences in fertility would have to be huge and thus entirely out of line with the hypothesis which requires that only a small increase be present and operating in order to maintain the gene frequencies of a pair of alleles in polymorphic balance. The observed differences are of the right magnitude and all in the same direction and therefore compatible with the hypothesis that the TSD heterozygote has a selective advantage over the presumed homozygous normal. But, unless either the fitness differential or the study sample is large enough to produce statistically significant differences, the probability of sampling variation must be kept in mind.

By this approach, then, the evidence cannot be considered as decisive and at best is only suggestive. But, since no reasonable support has been found for all the other logical hypotheses, including that of genetic drift, it is, perhaps, not idle to examine how ancillary and indirect evidence may bear on the hypothesis of heterozygote advantage.

Some evidence in favor of the heterozygote advantage theory is offered by the demonstration that, on the whole, the TSD sibships have significantly better survival than the control sibships. It appears that this advantage is largely due to the contribution of the U. S. born. This is surprising, especially since the fertility differential, although not significant, showed a definite gradient (Table 5), being highest for siblings born outside the United States who survived to reproductive age, and becoming negligible when total siblings born in the United States were considered. One possible explanation for this is that the data for the non-U. S. born group are not as reliable as those for the U. S. born, or perhaps a number of unknown factors are at play. Be that as it may, it is not unreasonable to attribute differential survival to resistance to some adverse situation, e.g. disease, conferred by the TSD gene. Such an explanation is compatible with the hypothesis of heterozygote advantage.

Historical perspective may also furnish some helpful information. At least three culturally and ethnically distinct Jewish groups are recognized in our times. These date back to the first century A.D., if not earlier. One group, known as the Ashkenazi, are those Jews who, after having left Palestine, dispersed in central, eastern, and western Europe, and includes their descendants who emigrated from there to North and South America, South Africa, and Australia. Another group, the Sephardi, lived in the countries around the Mediterranean, including the European part of Turkey. A third group, the Oriental Jews, live in Asia Minor, Iraq, Iran, and Yemen. It is generally agreed that the three Jewish groups achieved cultural and perhaps genetic individuality during the two thousand years of the diaspora. The rise of the frequency of

the TSD gene in one of these groups can also be assumed to have been a part of the same process.

The conquest of Jerusalem by Titus during the first century A.D. is a historical landmark which altered fundamentally the course of life and cultural activity of the Jewish people. Although there were large numbers of dispersed Jews before the Roman conquest of Jerusalem, it is only since then that the mass exodus began. One may argue that the Jewish people who immigrated to central, eastern, and western Europe, especially those who ultimately settled in Poland and the Baltic States, developed a way of life subject to certain selective pressures which favored the rise of the TSD gene, while those who stayed around the Mediterranean and in the Oriental part of Palestine pursued a life which did not favor any appreciable change of the status quo. Post (1965) suggests that the continuous habitat of most Jewish populations for several millennia in cities which have greater exposure to infectious and contagious diseases than rural populations, along with greater tolerance and concern of Jews for illness, may have provided an ecological environment different enough from that of the Gentiles to result in differential rates of natural selection between Jews and Gentiles.

It should be noted that TSD is not the only genetic disorder which has a uniquely high frequency among the Ashkenazi Jews. Gaucher's disease, Niemann-Pick disease, and possibly other rare metabolic disorders are known also to have a very high frequency among them and a much lower frequency among the other Jewish groups and non-Jewish populations. It is interesting that the antecedents of the majority of Jewish cases of both Gaucher's disease and Niemann-Pick disease in the United States are also traced to the northeastern provinces of Poland and the Baltic States. This may be explained on the grounds that all three lipid storage diseases are subject to the same unknown selective force and share the same polymorphic properties.

The historical argument can be carried one step further by estimating the magnitude of a presumed selective advantage required to raise the TSD gene frequency from 0.0013 at the end of the first century A.D., when the mass emigration of the Jews began, through 50 generations to the late nineteenth century, when TSD was recognized as occurring chiefly among the Ashkenazi Jews with a gene frequency of 0.0126. The following model was suggested by Dr. Alfred Naylor.

If the frequency of the TSD gene is q and the fitness S, then

	TT	Tt	tt
Frequency	p^2	$2pq$	q^2
Fitness	1-S	1	0

After selection

$$q' = \frac{(\tfrac{1}{2})\,2pq}{1 - Sp^2 - q^2} \simeq \frac{q}{1 - S} \quad (\text{if } p \simeq 1)$$

$$\Delta q' = \frac{Sq}{1 - S} \simeq \frac{dp}{dt}$$

and $$\frac{dp}{q} = \left(\frac{S}{1-S}\right) dt = d\log_e q$$

Integrating both sides with respect to time and gene frequency, we have

$$\frac{S}{S-1} t \int_{t_1(\text{present time})}^{t(50\text{ generations})} = \log_e q \int_{q_1(\text{non-Jewish frequency})}^{q_2(\text{Ashkenazi frequency})}$$

Substituting,

$$50\frac{S}{S-1} = \log_e \frac{0.0126}{0.0013} = 2.3$$

$$\frac{S}{S-1} = 0.046$$

$$S = \frac{0.046}{1+0.046} = 0.044$$

It appears, then, that a selective advantage of about 4½% would suffice, under the assumptions, to raise the gene frequency to its present level among the Ashkenazi Jews. This is not too different from the over-all advantage of about 6% estimated from our data and, therefore, compatible with the hypothesis of heterozygote advantage.

The most promising approach is, of course, through demographic studies of the east European Ashkenazi communities in the areas where the antecedents of the TSD cases lived for many generations. If a selective agent is involved, its identification may possibly be achieved through an analysis of the political, social, ecologic, and epidemiologic forces uniquely influencing these communities. The recent genocide of the Jewish peoples during World War II, the destruction of records, and the rapidly changing traditional Jewish way of life make this undertaking extremely difficult. But in another generation, whatever evidence still remains will disappear altogether. Demographic studies of the type mentioned above have been initiated by us and are now in progress.

SUMMARY

It is now well established that the birth incidence of Tay-Sachs disease (TSD) is a hundred times higher (and the gene frequency ten times higher) among the Ashkenazi Jews than among other Jewish groups and non-Jewish populations. There is no evidence that differential breeding pattern, genetic drift, or differential mutation rate can explain the difference in gene frequency distribution. The possibility of differential fertility of the heterozygote is examined at length. The reproductive performance of the grandparents of Jewish infants affected with TSD is compared with that of an appropriate control group. Although the differences in reproductive performance between the two groups are not statistically significant, the results suggest, but do not prove, that the Jewish heterozygote enjoys an over-all reproductive advantage of about 6% over the presumed homozygous normal. This advantage appears to

be greatest for offspring born outside the United States and surviving to reproductive age, diminishes for offspring born in the United States and surviving to reproductive age, and becomes negligible when total offspring born in the United States is considered. Survival to age 21, however, is significantly higher among TSD sibships than among control sibships, and this finding corroborates the heterozygote advantage hypothesis. Historical evidence also appears to corroborate the hypothesis and to place the rise of the TSD gene among the Ashkenazi Jews in historical times, perhaps during the early centuries of the diaspora.

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